SECTION 4.0

COMPLIANCE WITH UNITED STATES AND CANADIAN CLINICAL TRIAL REGULATIONS AND GOOD CLINICAL PRACTICE (GCP)

CREST was conducted at 119 sites in the United States and 10 sites in Canada. The following sections delineate responsibilities for conduct of the trial in the United States and Canada.

4.1 CREST Compliance in the United States

In the United States, CREST is conducted under IDE G000080 as an investigator-sponsored study. The investigator sponsors were Dr. Robert Hobson (deceased) and Dr. Thomas Brott with the support of the UMDNJ (University of Medicine and Dentistry at New Jersey). Responsibilities performed by Dr. Hobson and Dr. Brott at UMDNJ are those listed in **Section 4.1.1**.

Abbott Vascular, the former IDE sponsor of CREST, officially transferred sponsorship of the trial to Dr. Hobson (G000080/S23). A Collaborative Agreement was signed by Dr. Hobson at UMDNJ and Abbott Vascular on April 25, 2003 outlining the duties and responsibilities for conduct of CREST. Since the transfer of IDE G000080 to UMDNJ, Abbott Vascular supported CREST as the manufacturer of the investigational devices and assumed responsibilities identified in **Section 4.1.2**.

Abbott Vascular also assumed additional responsibilities for CREST activities in the United States and Canada providing assistance to UMDNJ as described in **Section 4.3.** These responsibilities pertain to United States and Canadian trial activities.

4.1.1 CREST Responsibilities in the U.S. – UMDNJ

1) Conducting CREST under all applicable U.S. regulations and guidance of the U.S. Food and Drug Administration, including:
   - 21 CFR Part 812, Investigational Device Exemptions
   - 21 CFR Part 50, Protection of Human Subjects
   - 21 CFR Part 54, Financial Disclosure By Clinical Investigators
   - 21 CFR Part 56, Institutional Review Boards

2) Obtaining and reviewing copies of IRB/REB approvals and renewals;

3) Notifying Abbott Vascular to ship devices to investigational sites when appropriate approvals have been obtained;

4) Selecting and qualifying investigational sites;

5) Selecting and qualifying site investigators, including obtaining sufficient financial disclosure information;

6) Obtaining signed Investigator Agreements from all participating investigators;

7) Ensuring appropriate investigational site monitoring;

8) Ensuring appropriate investigational site training for investigators and staff;

9) Ensuring compliance of investigational sites and investigators with the CREST protocol;

10) Verifying that appropriate written Informed Consent(s) was obtained for each enrolled subject;

11) Submitting changes to the investigational plan to the FDA or other applicable regulatory agencies;

12) Submitting appropriate reports as required by 21 CFR Part 812.150 (including but not limited to unanticipated adverse device effects, withdrawal of IRB/FDA/regulatory agency approval, annual progress reports, recall information, final reports, and device use without informed consent);

13) Collecting and maintaining documentation as required by 21 CFR Part 812.140 (including but not limited to duplicate copies of correspondence, device shipment information, subject records and case reports forms, adverse device effects, and other regulatory records related to CREST); and

14) Conducting CREST according to the relevant parts of the ICH Guidelines for Good Clinical Practice (GCP), the International Conference on Harmonization and the Declaration of Helsinki.

4.1.2 CREST Responsibilities in the U.S. - Abbott Vascular

1) Manufacture of investigational devices used in CREST in compliance with 21 CFR Part 812.50 and 21 CFR Part 820;

2) Shipment of investigational devices to clinical sites upon authorization from the UMDNJ Administrative Center;

3) Investigating complaints from participating investigational sites and investigators that an investigational device failed to perform as intended;

4) Determining the necessity of a recall, conducting any device recovery activities, and implementing any resulting device design or manufacturing modifications; and

5) Ensuring return of all investigational devices at the conclusion of the trial or in the event of investigational site termination and/or suspension.

4.2 CREST Compliance in Canada

Abbott Vascular sponsored CREST at 10 investigational sites in Canada. CREST was conducted in Canada in compliance with the Canadian Medical Device Regulations (SOR98 - 282), Part 3 Medical Devices for Investigational Testing Involving Human Subjects (Sections 79 - 88) administered by the Canadian Therapeutic Products Directorate.

The investigational devices used in CREST, the Acculink and RX Acculink Carotid Stent Systems and the Accunet and RX Accunet Embolic Protection Systems, were approved for sale in Canada under the Investigational Testing Authorizations (ITA) 39451, 57394, 82838, and 94308 issued by the Health Canada Therapeutic Products Directorate.

Abbott Vascular assumed full responsibility for all requirements specified in Sections 79-88 of the Canadian Medical Device Regulations (SOR98 - 282). Specifically, Abbott Vascular fulfilled the roles identified in **Section 4.2.1** in the conduct of CREST in Canada and delegated clinical trial activities identified in **Section 4.2.2** to UMDNJ.

4.2.1 CREST Responsibilities in Canada - Abbott Vascular

1) Manufacture of investigational devices used in CREST in compliance with CAN/CSA ISO 13485;

2) Obtaining appropriate Investigational Testing Authorizations and submitting changes to the investigational plan to Health Canada Therapeutic Products Directorate, as necessary;

3) Shipment of investigational devices to clinical sites and maintenance of distribution records per SOR98 - 282, Sections 52 - 56. Shipment was only initiated following authorization from the UMDNJ Administrative Center;

4) Investigating complaints from participating investigational sites and investigators that an investigational device failed to perform as intended per SOR98 - 282, Sections 57 - 58;

5) Submitting Mandatory Problem Reports, as necessary, per SOR98 - 282, Sections 59 - 61.1;

6) Determining the necessity of a recall, conducting any device recovery activities, and implementing any resulting device design or manufacturing modifications per SOR98 - 282, Sections 63 - 65.1;

7) Ensuring return of all investigational devices at the conclusion of the trial or in the event of investigational site termination and/or suspension.

4.2.2 CREST Responsibilities in Canada - UMDNJ

1) Conducting CREST according to the relevant parts of the ICH Guidelines for Good Clinical Practice (GCP), the International Conference on Harmonization and the Declaration of Helsinki. In addition, the trial was conducted under relevant parts of U.S. FDA regulations contained in 21 CFR Parts 50, 54, 56, and 812;

2) Obtaining and reviewing copies of IRB/REB approvals and renewals;

3) Notifying Abbott Vascular to ship devices to investigational sites when appropriate approvals have been obtained;

4) Selecting and qualifying investigational sites;

5) Selecting and qualifying site investigators, including obtaining sufficient financial disclosure information;

6) Obtaining signed Undertakings (Investigator Agreements) from all participating investigators;

7) Ensuring appropriate investigational site monitoring;

8) Ensuring appropriate investigational site training for investigators and staff;

9) Ensuring compliance of investigational sites and investigators with the CREST protocol;

10) Verifying that appropriate written Informed Consent(s) was obtained for each enrolled subject;

11) Collecting and maintaining documentation as required by 21 CFR Part 812.140 (including but not limited to duplicate copies of correspondence, device shipment information, subject records and case reports forms, adverse device effects, and other regulatory records related to CREST).

12) Conducting CREST according to the relevant parts of the ICH Guidelines for Good Clinical Practice (GCP), the International Conference on Harmonization and the Declaration of Helsinki.

4.3 Collaborative Efforts of Abbott Vascular with UMDNJ

Abbott Vascular has collaborated with the UMDNJ Administrative Center and the investigator sponsors, Dr. Hobson and Dr. Brott by providing assistance for:

1) Investigational site monitoring in the United States and Canada to assist UMDNJ in ensuring site compliance with the CREST protocol and with relevant aspects of 21 CFR Part 814.

2) Monitoring in the United States and Canada to ensure that the data being submitted in this PMA Supplement are consistent with industry standards for Good Clinical Practice.

3) Verification of data received from the University of Alabama, the designated Statistical Data Management Center, for analysis by Abbott Vascular to ensure integrity of data.

4.4 Institutional Review Board and Subject Informed Consent

The CREST protocol and Informed Consent documents were reviewed and approved by the CREST Executive Committee and the Food and Drug Administration. Each clinical center participating in CREST subsequently obtained approval from their reviewing IRB/REB for each revision of the CREST protocol in which they participated and all appropriate revisions of the Informed Consent document prior to its use for subject enrollment.

All subjects were required to sign the appropriate Informed Consent document prior to enrollment in CREST and during the trial, as appropriate. Subjects were eligible for enrollment after having met all inclusion/exclusion criteria as determined by laboratory, neurologic, and duplex ultrasound and/or angiographic evaluation.
Copies of all signed Informed Consent documents for all subjects participating in CREST are maintained by each participating site and are subject to verification during routine monitoring of subject records.